REMARKS

Claims 1 – 9, 11, 24, and 27 - 30, as amended and new claims 31 – 39 are pending in the application. Claims 10 and 12 – 20 are withdrawn from consideration. Claims 21 – 23, 25, and 26 are canceled without prejudice. The amendment to claim 1 removes the particle size limitation and the dissolution profile which were added to the claims in a previous amendment. The amendment to compound 2 is a minor amendment reflecting the amendment made in claim 1. The amendments to claims 6 and 27 excised one particular combination that did not include a disintegrant. New claims 31 – 34 contain the dissolution profile limitations that were excised from claim 1. New claims 35 – 39 represent method of preparing granulates of ospemifene using the general methodology disclosed in the specification. Therefore no new matter is presented.

Claims 1-9, 11, and 24-30 stand rejected as being unpatentable over Furuya. This rejection is respectfully traversed.

In the Amendment and Reply dated December 18, 2007, Applicants clearly set forth the deficiencies of Furuya and provided detailed reasoning why one of ordinary skill in the art would not be able to pick and choose among thousands of variables the specific combination of techniques and excipients that produce Applicants' claimed composition solving a problem not recognized by the prior art. For example, Furuya discloses thousands of potential active ingredients that can potentially be combined with a GnRH agonist to prevent or treat a series of diseases such as breast cancer, menopausal syndrome, precocious puberty, etc. Furuya also discloses general methodologies and known excipients used in making pharmaceutical formulations. Furuya does not teach or suggest a solid drug formulation comprising granulates containing 30 to 90 mg of ospemifene, in combination with one or more intra-granular excipients, wherein at least one intra-granular excipient is a disintegrant, wherein at least 80% of the formulation is dissolved within 30 minutes after subjecting said formulation to dissolution testing at pH 9.8 according to the USP 24 paddle method.

Applicants respectfully submit that the Examiner has broken the invention into its component parts and found a reference corresponding to many (but not all) of the claim

limitations, but failed to provide the necessary suggestion or motivation, before the invention itself, to make the new formulation.

The "as a whole" instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might successfully break an invention into its component parts, then find a prior art reference corresponding to each component. This line of reasoning would impart hindsight into the obviousness determination by using the invention as a roadmap to find its prior art components. Further, this improper method would discount the value of combining various existing features or principles in a new way to achieve a new result – often the essence of invention.

Contrary to this reasoning, section 103 requires assessment of the invention as a whole. This "as a whole" assessment of the invention requires a showing that an artisan of ordinary skill in the art at the time of the invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would have selected the various elements from the prior art and combined them in the claimed manner.

As the Federal Circuit explained recently in *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.,* 86 USPQ 2d 1196 (Fed. Cir. 2008), a flexible teaching, suggestion, or motivation (TSM) test remains the primary guarantor against a non-statutory hindsight analysis, such as is occurring in this case. The alleged teachings of Furuya are noteworthy for what they lack. For example, Furuya provides:

- no working examples except for one drug combination of luprorelin acetate and raloxifene;
- no disclosure relating to dissolution characteristics of the listed drugs; and
- no mention of ospemifene being a preferred embodiment or of the superior profile imparted by granulating ospemifene with an intragranular disintegrant.

There is no finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinary skilled artisan of obviousness.

A finding of obviousness requires that the prior art both suggest the invention and provide one of ordinary skill with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988). Secondary considerations such

as unexpected results must be considered if present. *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1538-39, 218 USPQ 871, 879 (Fed. Cir. 1983); *In re Merck & Co., Inc.,* 800 F.2d 1091, 1096, 231 USPQ 375, 378 (Fed. Cir. 1986). In this case, Applicants' claimed formulation, as amended, is not suggested by the prior art and achieves unexpected results.

Assuming for the sake of argument that the Examiner could provide objective evidence of motivation to select ospemifene, granulate the drug with at least one intragranular excipient comprising a disintegrant, the invention possesses unexpected results. Applicants' unexpected results lie in the discovery that the claimed formulation possesses a far superior *in vitro* dissolution profile over tablets of ospemifene made by direct compression techniques. As seen in Figure 1 in the specification, the particular granulated formulation claimed herein shows greater than 80% dissolution in the particular *in vitro* dissolution tests and substantially complete dissolution within two hours. In contrast the ospemifene tablets made by direct compression show approximately 60% dissolution at the thirty minute mark and no more than 80% dissolution at the two hour time point.

The Examiner cites *In re Aller*, 220 F.2d 454, 456; 105 USPQ 233, 235 (CCPA 1955) for the proposition that where general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. For example, in *Heller* the prior art disclosed a process for decomposing isopropyl benzene hydroperoxide and provided a working example where the process was conducted at a temperature of 100º C and with a 10% sulphuric acid solution. The appellants attempted to claim an identical process except that the temperatures were lower and the sulphuric acid concentrations were higher than the prior art reference. However, the appellants did not appear to show actual improved results over the prior art reference (phenol yields 83.7% v. 75%; 71% v. 60% acetone yields, although prior art silent; reaction times of 20 min to 3 hours v. 1.5 hour reaction times).

The CCPA stated that "[n]ormally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability

to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." *Aller* at p. 235.

First, with regard to *Aller*, it should be noted that with "such 'rules of patentability' (and the ever-lengthening list of exceptions which they engender) is that they tend to becloud the ultimate legal issue – obviousness – and exalt the formal exercise of squeezing new factual situations into pre-established pigeonholes. Additionally, the emphasis upon routine experimentation is contrary to the last sentence of section 103." *In re Yates*, 663 F.2d 1054, 1056 (CCPA 1981).

Second, the facts differ from the instant case. Applicants are not simply changing the temperature of a process and the concentration of one of the reaction conditions to obtain a statistically insignificant process improvement. As noted above, the cited prior art, Furuya, discloses thousands of active ingredients and large generic disclosures of pharmaceutical excipients to solve a different problem, e.g. improving the preventative or therapeutic effect of a GnRH agonist on various diseases and improving the quality of life of the patient. There is nothing in Furuya disclosing how granulation and the use of intragranular disintegrants can improve the dissolution of an ospemifene formulation containing 30-90 mg of active ingredient. Further, there is nothing in Furuya disclosing that such a formulation would possess *unexpectedly superior in vitro* dissolution characteristics. One must engage in impermissible hindsight reconstruction using Applicants' invention as a guide in order to arrive at the unique composition to solve the problem faced by Applicants and not recognized by the cited prior art.

The Examiner alleges that the "prior art reads on the instant application as claimed." Applicants respectfully disagree with this comment in two ways. First, properly understood, only claims can read on the prior art, not vice versa. Second, it is applicants' understanding that this term "reads on" is only properly used in an anticipation context. If our understanding is correct, then we object to the use of the phrase "read on" in this context. A reference is not anticipatory if one must select from several large laundry lists of components to arrive at the specific claimed combination of elements. Further, since Furyua provides no finite, small or easily traversed number of

options for one to select the narrowly-claimed composition to solve the particular problem, Furuya is deficient in rendering prima facie obvious the claimed invention.

In commenting on the evidence of unexpected superior results, the Examiner relates that "applicants are claiming a formulation, not a method of making a formulation. Evidence of unexpected results using specific techniques is directed to a method of making a formulation."

Applicants respectfully disagree and submit that the in vitro dissolution profile of a pharmaceutical formulation has a direct bearing on the bioavailability and the effectiveness of a drug product. If a particular formulation is shown to have a superior in vitro dissolution profile, then that is evidence that the formulation itself is patentable regardless of how it is made. Applicants further point out that using the Examiner's own position, the in vitro dissolution data is evidence that new method claims 35 – 39 are patentable.

In summary, Applicants argue: (1) no *prima facie* case of obviousness has been made since there is no motivation to select the unique combination of ingredients to come up with the claimed formulation for solving the problem at hand; and (2) even if a *prima facie* case had been made, the specification establishes clear evidence of unexpected results created by the claimed invention when compared to similar formulations made direct compression techniques and this evidence has not been rebutted by the Examiner. None of the cases cited by the Examiner contradicts the line of cases and analysis provided by Applicants above.

One must engage in impermissible hindsight reconstruction using applicants' disclosure as a guide to arrive at the claimed invention. In short, there is no teaching or suggestion of the claimed invention as amended.

Therefore, Applicants submit that the claimed invention, as amended, is patentable over Furuya and respectfully request reconsideration and withdrawal of the obviousness rejection.

Applicants thank the Examiner for his consideration of this case and submit that the case is in condition for immediate allowance. If the Examiner believes that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at 734-302-6042.

Respectfully submitted,

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